Articles

Antibiotic Resistance in Bacterial Urinary Tract Infections, 1991 to 1997

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This study assessed changing patterns of antibiotic resistance in *Escherichia coli* urinary tract infections at a university student health center during three periods: the first 6 months each of 1991, 1994, and 1997. Urine culture and sensitivity results were taken from available medical records of female patients having urine cultures during the three periods (1991, *n* = 739; 1994, *n* = 938; 1997, *n* = 863); age and ethnicity were also noted. In *E. coli* isolates (the majority of positive cultures), resistance to four antibiotics changed significantly: ampicillin (30% to 45% to 39%), carbenicillin (29% to 42% to 39%), tetracycline (29% to 40% to 23%), and trimethoprim/sulfamethoxazole (15% to 32% to 15%). The results raise questions regarding the future clinical reliability of several commonly used antibiotics in the treatment of urinary tract infection.

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Bacterial infection of the urinary tract is a common health problem in young women.[1] *Escherichia coli* accounts for approximately 80% of uncomplicated cystitis in this group, with *Staphylococcus saprophyticus* reportedly causing another 5%–15%.[2] Treatment regimens for urinary tract infection (UTI) in the outpatient setting have often consisted of trimethoprim-sulfamethoxazole (TMP/SMX) or ampicillin, both of which may become less effective as bacterial resistance to various antimicrobials becomes more common.[2–11] Resistant bacterial strains are emerging and spreading throughout the world, mainly because of the extreme genetic plasticity of the microorganisms themselves, the mobility of the world population, and the heavy selective pressures of antimicrobial use.[10,12]

Increased risk of UTI is found in women who are sexually active, those using diaphragms with spermicide, those who delay postcoital urination, and those with a recent history of urinary tract infection.[13–15] The university health service is an ideal setting for collecting data on a young, sexually active population. A 1993 study[16] of UTI in college women in New York indicated that amoxicillin and the cephalosporins were no longer effective first-line UTI treatments, but that nitrofurantoin and TMP/SMX remained good choices.

At the UCLA Student Health Center, female patients who present with symptoms of UTI are treated empirically with ampicillin or TMP/SMX, after being instructed to collect a clean-catch midstream urine specimen. A urinalysis and urine culture are performed on each specimen. On all urine specimens with pure growth of a known uropathogen, further workup includes identification, colony count, and antimicrobial susceptibility testing. Patients are instructed to return for follow-up treatment if symptoms persist. The policies and practices for obtaining cultures have not changed for the past 7 years.

The aim of this retrospective chart review was to compare the results of urine cultures obtained during three time periods, the first 6 months each of 1991, 1994, and 1997, to evaluate the change in *E. coli* antibiotic resistance over a 6-year period and its potential implications for treatment of UTI.

Methods

Urine culture results were obtained from the medical records of all female patients at the UCLA Student Health Center who had urine cultures performed during January through June of 1991, 1994, and 1997. We analyzed the first culture obtained from each patient within each of the time periods, regardless of result. Information collected included patient's date of birth and race/ethnicity, date of first culture, organisms isolated (if any), colony count, and antibiotic susceptibility results, if performed. If more than one organism was isolated, results were recorded as "mixed culture." We defined a

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ABBREVIATIONS USED IN TEXT
TMP/SMX = trimethoprim-sulfamethoxazole
UTI = urinary tract infection.

positive culture as pure growth of a known uropathogen with a colony count of greater than 100,000 colony-forming units per milliliter.

Laboratory testing was performed at the UCLA Student Health Center Laboratory. Identification of Gram-negative organisms and antibiotic susceptibility testing were performed using the Baxter Microscan system (Baxter Diagnostics, McGaw Park, IL), according to the manufacturer's guidelines. The antibiotics tested and the concentrations used to define resistance were as follows: ampicillin, ≥128 µg/ml; amoxicillin/clavulanic acid, >16/8 µg/ml; carbenicillin, >64 µg/ml; cephalothin, >16 µg/ml; ciprofloxacin, >2 µg/ml; nitrofurantoin, >64 µg/ml; tetracycline, ≥128 µg/ml; and TMP/SMX, >2/38 µg/ml. Organisms with "intermediate" levels of resistance were not included in the percentages of resistant organisms. No changes in laboratory or testing methods were made during the study period.

Results

Study Populations: 1991 versus 1994 versus 1997

A total of 790 female patients had urine cultures ordered in the first half of 1991; 51 patient charts were missing or incomplete, leaving 739 (94%) charts from 1991 for analysis. In the first six months of 1994, urine cultures were ordered on 945 women; seven charts were missing or incomplete, leaving 938 (99%) charts to be analyzed from 1994. Medical records from the first half of 1997 were available on all 863 (100%) female patients who had urine cultures.

The study populations in 1991, 1994, and 1997 were similar with respect to age (median age 22.0, 23.0, and 22.3 years, respectively), but ethnicity varied somewhat; an increase in the percentage of Asians (19.1%, 26.7%, and 29.9%) was offset by a decrease in the percentage of whites (53.0%, 44.7%, and 38.4%, respectively).

Culture results were similar between the three populations. In 1991, 1994, and 1997, *E. coli* was the sole isolate in 31%, 33%, and 29% of cultures, respectively; a different single pathogen was isolated in 14%, 11%, and 9%; and a result of no growth, mixed organisms, *Lactobacillus* species, or *Staphylococcus epidermidis* was reported in 55%, 56%, and 63% of cultures.

Positive Cultures

There were 286 positive cultures in the 1991 group (69% *E. coli*, 9% other Gram-negative bacilli, 3% *Staphylococcus saprophyticus*, and 19% other single organisms). In the 1994 patients, 343 had positive cultures (75% *E. coli*, 7% other Gram-negative bacilli, 3% *S. saprophyticus*, and 15% other single organisms). In 1997, 246 patients had positive cultures (81% *E. coli*, 8% other Gram-negative bacilli, 5% *S. saprophyticus*, and 6% other single organisms). The percentage of positive cultures with *E. coli* isolates increased significantly between 1991 and 1997.

TABLE 1.—*Demographic characteristics and E. coli antibiotic resistance in patients with E. coli urinary tract infections*

	1991 (n = 198)	1994 (n = 263)	1997 (n = 208)
Age (%)			
18–21 years	49.0	47.9	48.6
22–25 years	32.8	33.8	37.5
≥26 years	18.2	18.3	13.9
Ethnicity (%)			
White (non-Hispanic)	54.0	41.1	35.6*†
Asian	19.7	33.1	33.6*†
Hispanic	11.6	12.9	17.3
Black	8.6	8.0	5.3
Other	2.0	1.1	5.8
Data missing	4.0	3.8	2.4
Antibiotic resistance (%)			
Ampicillin	30.3	44.9	38.9*†
Amoxicillin/Clavulanic Acid	4.5	1.5	0.5
Carbenicillin	29.3	41.8	38.5*†
Cephalothin	16.7	14.8	15.4
Ciprofloxacin	0.5	0.0	0.0
Nitrofurantoin	0.0	0.0	0.0
Tetracycline	28.8	40.3	22.6‡
Trimethoprim/sulfamethoxazole	14.6	31.9	15.4‡

Statistically significant difference at $P < 0.01$: *1991/1994, †1994/1997.

We further examined the three groups of patients with positive *E. coli* cultures; the results of that comparison are shown in Table 1. The three groups did not differ significantly with respect to age, but the same ethnic differences observed in the total study populations were seen. There was a statistically significant drop in the percentage of white students, with a corresponding increase in the percentage of Asians from 1991 to 1994 and 1997.

Notable differences were apparent in the antibiotic sensitivity results between the 1991, 1994, and 1997 populations. While resistance to amoxicillin/clavulanic acid, ciprofloxacin, nitrofurantoin, and cephalothin did not differ significantly between the three groups, there were significant changes in resistance to the other antibiotics tested. Ampicillin resistance increased from 30% in 1991 to 45% in 1994 ($P < 0.05$), then decreased to 39% in 1997. Carbenicillin resistance increased from 29% in 1991 to 42% in 1994, and decreased slightly to 39% in 1997 ($P < 0.05$). Tetracycline resistance showed a significant increase from 29% in 1991 to 40% in 1994, but then decreased to only 22.6% in 1997. TMP/SMX resistance significantly increased from 14% resistance in 1991 to 31% in 1994, then dropped to 15% in 1997 (Figure 1).

In all three groups, 44% of *E. coli* isolates were sensitive to all tested antibiotics. Another common pattern

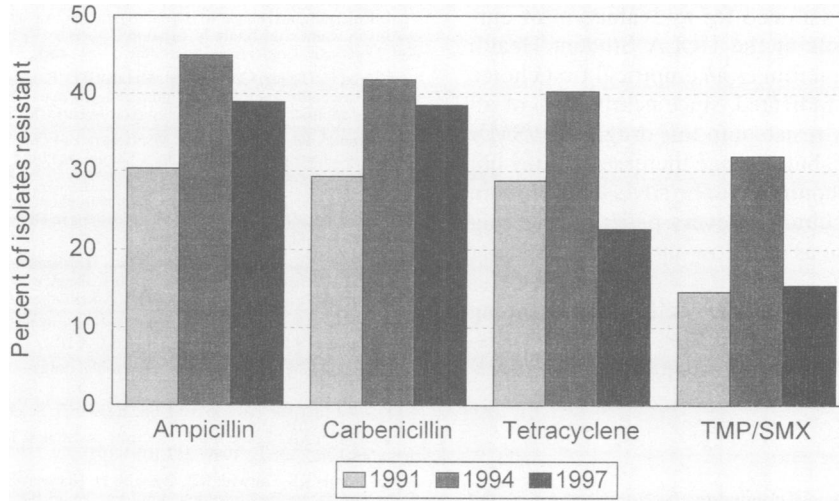

Figure 1.—*E. coli* antibiotic resistance, 1991, 1994, and 1997.

included ampicillin, carbenicillin, and tetracycline resistance occurring together in 17%, 24%, and 15% of isolates in 1991, 1994, and 1997, respectively.

Discussion

The increasing resistance of *E. coli* organisms in UTI to commonly used antibiotics was demonstrated in the first 3 years of this study, with four antibiotics (ampicillin, carbenicillin, tetracycline, and TMP/SMX) showing a marked increase in resistance over the first 3-year period. In the following 3 years, however, the trend did not continue. Resistance to ampicillin and carbenicillin leveled off (1994/1997 differences were not statistically significant), and tetracycline and TMP/SMX both decreased in resistance to return approximately to 1991 levels.

The reasons for the diminishing resistance to two commonly used antibiotics from 1994 to 1997 may include a change in usage by providers. Results of a recently published Finnish study[17] of erythromycin resistance in group A Streptococci strongly suggest that a widespread reduction in the use of certain antibiotics may be effective in lowering the frequency of resistant organisms in the population. In an earlier study, Ballow and Schentag[3] reported a decrease in *E. cloacae* resistance to ceftazidime in hospitalized patients following restricted usage of the drug. Prescription drug utilization data from the past 6 years at the UCLA Student Health Center are not available, indicating a need for further studies examining the correlation between antibiotic usage and organism resistance.

The two most commonly used antibiotics for treatment of UTI at the UCLA Student Health Center are ampicillin and TMP/SMX. In 1994, ampicillin was ineffective against 45% of *E. coli* isolates and TMP/SMX was ineffective against 32% of *E. coli* isolates. In 1997, TMP/SMX resistance dropped to 15% and ampicillin resistance was 39%. Further analysis shows that 77 of 263 isolates in 1994 (29%) were resistant to both ampicillin and TMP/SMX, but in 1997 only 28 (13%) of isolates were resistant to both antibiotics. Patterns of resistance as seen here may be due to single genetic mutations in the *E. coli* organisms.[9] No *E. coli* isolates were found to be resistant to every tested antibiotic. However, factors such as toxicity, limited spectrum, and high cost may make some antibiotic choices undesirable.

It is interesting to note that resistance to nitrofurantoin was nonexistent in all three periods. Years ago, this drug was commonly prescribed for UTI because it concentrates in the urine, where it is most effective. It has fallen out of favor in recent years, perhaps due to side effects and the development of new bacteriocidal antibiotics. However, from our results, it appears that nitrofurantoin should be reexamined as a first-line drug for UTI.

Since urinalysis results were not collected as part of this study, we do not know what proportion of patients whose urines were cultured or had positive cultures also had pyuria or other indications that the *E. coli* isolates evaluated were clinically significant.

We did not find age to be a factor in the results. Older females with presumably greater opportunity for antibiotic exposure and resistance did not have any more resistance than younger women. It seems that resistant urinary pathogens are widely distributed throughout the population. The differences in ethnic composition in the three groups most likely reflect the population of the UCLA student body as a whole (in recent years, an increasing number of Asian students have enrolled at the University).

Conclusion

Bacteria with antimicrobial resistance are associated with more morbidity, mortality, and cost (as measured by hospitalization and death rates) than are their drug-susceptible counterparts.[18] It is important, therefore, to examine treatment strategies with attention to preventing increased bacterial resistance, as well as to effective treatment and cost containment.

This study indicates a need for re-evaluation of current treatment protocols at the UCLA Student Health Center. The use of ampicillin as an empirical first choice for UTI is clearly not indicated, since nearly 40% of all *E. coli* infections were resistant to this drug. TMP/SMX may be a better choice, but if usage increases, it may not remain satisfactory. It continues to be advisable to obtain a urine specimen for culture on every patient presenting with UTI symptoms, so as to follow-up on incomplete or ineffective treatment.

Further studies that examine the relationships among clinical symptoms, antibiotic usage, organism resistance, and clinical outcomes would be valuable to determine appropriate treatment strategies.

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